ANGELIQ - estradiol and drospirenone tablet, film coated
Bayer HealthCare Pharmaceuticals Inc.

Rx only
PRESCRIBING INFORMATION

Boxed Warnings

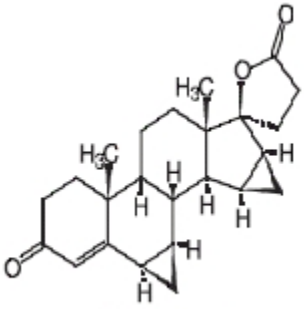
Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See WARNINGS, Cardiovascular disorders and Dementia.) The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo (see CLINICAL PHARMACOLOGY, Clinical Studies and WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer.) The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens alone and during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.) Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials, and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

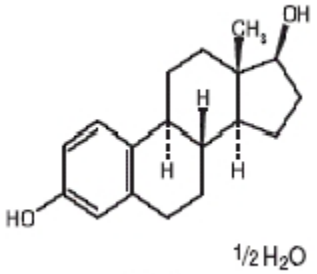
ANGELIQ TABLETS provide a hormone regimen consisting of film coated tablets each containing 0.5 mg of drospirenone and 1 mg of estradiol. The inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, and ferric oxide pigment NF.

Drospirenone, (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3´,4´,6, 6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa[6,7:15,16]cyclopenta[a]phenanthrene- 17,2´(5H)-furan]-3,5´(2H)-dione (CAS) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

Estradiol USP, (Estra-1,3,5(10)-triene-3,17-diol,17ß), has a molecular weight of 272.39 and the molecular formula is $C_{18}H_{24}O_2$. The structural formulas are as follows:



Drospirenone



Estradiol

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol (E2) is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These will vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), through a negative feedback mechanism.

Drospirenone (DRSP) is a synthetic progestin and spironolactone analog with antimineralocorticoid activity. In animals and *in vitro*, drospirenone has antiandrogenic activity, but no glucocorticoid, antiglucocorticoid, estrogenic, or androgenic activity. Progestins counter estrogenic effects by decreasing the number of nuclear estradiol receptors and suppressing epithelial DNA synthesis in endometrial tissue.

Pharmacokinetics

Absorption
Serum concentrations of DRSP reach peak levels approximately 1 hour after administration of **ANGELIQ** and mean absolute bioavailability of DRSP ranges from 76–85%. Following oral administration, peak serum estradiol concentrations are typically reached 6–8 hours after dosing with **ANGELI**Q. The oral relative bioavailability of estradiol and DRSP following administration of **ANGELIQ** is 107% and 102%, respectively when compared to a combination oral suspension.

The pharmacokinetics of DRSP are dose proportional within the dose range of 0.5–4 mg. Following daily dosing of **ANGELIQ**, steady state DRSP concentrations were observed after 10 days. Mean accumulation ratios for estradiol and DRSP were 1.9 and 2.4, respectively. Mean concentrations at 2 hours for DRSP ranged between 5.9 and 6.7 ng/mL after treatment with **ANGELIQ** for 365 days. Mean steady state serum DRSP and E2 concentrations are shown in Figure 1, and a summary of primary pharmacokinetic parameters following the administration of 1mg E2/1mg DRSP for 28 days is presented in Table 1.

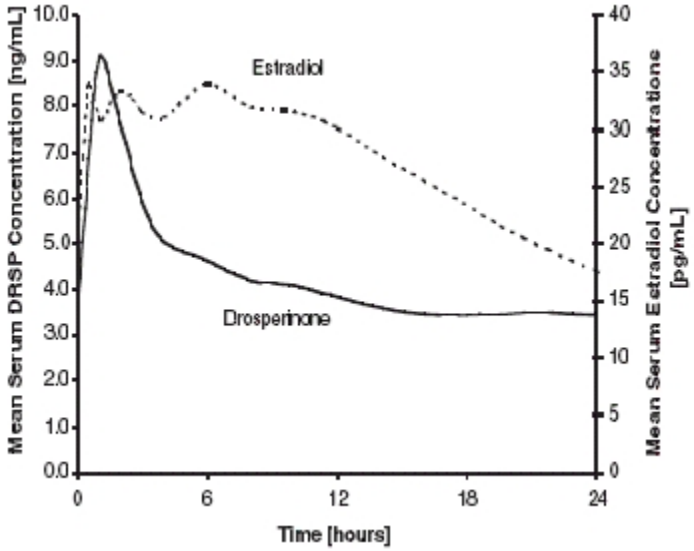


Figure 1: Mean steady state serum drospirenone and estradiol concentrations following daily oral administration of 1 mg E2/0.5 mg DRSP[11]DRSP levels are simulated based on data obtained after oral administration of 1 mg DRSP/1 mg Estradiol

Table 1: Mean Steady State Pharmacokinetic Parameters of Tablets Containing Drospirenone (1 mg)* and Estradiol (1 mg)

Drospirenone (Mean† ± SD‡)**					
Dose	**No. of Subjects**	**C_{max}§ (ng/mL)**	**t_{max}¶ (h) Median (range)**	**AUC# (0–24h) (ng•h/mL)**	**$t_{1/2}$Þ (h)**
1mg E2/1mg DRSP	14	18.3±5.55	1.0 (1.0–2.0)	208±83	42.3±21.3

Estradiol (Mean ± SD‡)					
Dose	**No. of Subjects**	**C_{max}§ (pg/mL)**	**t_{max}¶ (h) Median (range)**	**AUC# (0–24h) (pg•h/mL)**	**$t_{1/2}$Þ (h)**
1mg E2/1mg DRSP	14	43.8±10.0	2.5(0.5–12.0)	665±178	NAß
Estrone (Mean ± SD‡)					
Dose	**No. of Subjects**	**C_{max}§ (pg/mL)**	**t_{max}¶ (h) Median (range)**	**AUC# (0–24h) (pg•h/mL)**	**$t_{1/2}$Þ (h)**
1mg E2/1mg DRSP	14	245±50.6	4.0 (3.0–6.0)	3814±1159	23±6.2

*****Angeliq contains 0.5 mg DRSP
†arithmetic mean
‡SD = standard deviation.
§C_{max} = Maximum serum concentration,
¶tmax = time of maximum serum concentration,
#AUC = area under the curve
Þt1/2 = half-life,
ßNA = Not available,

Effect of Food:
The effect of food on the absorption and bioavailability of DRSP and E2 have not been investigated following the administration of **ANGELIQ**. However, clinical studies with different formulations containing DRSP or E2 have shown that the bioavailability of both drugs is not affected by concomitant food intake.

Distribution
The mean volume of distribution of DRSP is 4.2 L/kg. DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to SHBG (37%) and to albumin (61%), while only approximately 1%–2% is unbound.

Metabolism
Mean clearance of DRSP is 1.2 mL/min/kg. DRSP is extensively metabolized after oral administration. The 2 main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate, both of which are formed without the involvement of the cytochrome P450 system. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion
DRSP serum levels are characterized by a terminal elimination half-life of approximately 36–42 hours. Excretion of DRSP was nearly complete after 10 days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38% to 47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17% to 20% of the metabolites were excreted as glucuronides and sulfates. Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations
Geriatric: No pharmacokinetic studies were conducted in the geriatric population.

Pediatric: No pharmacokinetic study for **ANGELIQ** has been conducted in a pediatric population.

Gender: **ANGELIQ** is indicated for use in women only.

Race: No studies were done to determine the effect of race on the pharmacokinetics of **ANGELIQ**.

Patients with Hepatic Impairment: **ANGELIQ** is contraindicated in patients with hepatic dysfunction (also see BOLDED Warnings). The mean exposure to DRSP in women with moderate liver impairment is approximately three times the exposure in women with normal liver function.

Patients with Renal Impairment: **ANGELIQ** is contraindicated in patients with renal insufficiency (also see BOLDED Warnings).

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effects of DRSP on serum potassium levels were investigated in female subjects (n = 28, age 30–65) with normal renal function (11 patients), and mild (10 patients) and moderate (7 patients) renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium-sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLcr 30–50 mL/min) compared to those in the group with normal renal function. Serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50–80 mL/min) were comparable to those in the group with normal renal function (CLcr, >80 mL/min). DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in 5 of the 7 subjects who continued use of potassium sparing drugs during the study, individual mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs.

Drug Interactions

Effects of Drospirenone on Other Drugs

Metabolic Interactions
Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies (see Metabolism). In *in vitro* studies, DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3mg DRSP for 14 days did not affect the systemic clearance of the CYP2C19 substrate omeprazole (40 mg) and the CYP2C19 product 5-hydroxy-

omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrated that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*.

Two further clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4, were each performed in 24 healthy, postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady-state DRSP concentrations achieved after administration of 3 mg DRSP/day.

Based on the available results of *in vivo* and *in vitro* studies, it can be concluded that, at clinical dose level, DRSP is unlikely to interact significantly with cytochrome P450 enzymes.

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Co-Administration with Drugs that Have the Potential to Increase Serum Potassium
There is a potential for an increase in serum potassium in women taking drospirenone with other drugs that may affect electrolytes, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or non-steroidal anti-inflammatory drugs (NSAIDs).

Electrolytes were studied in 230 postmenopausal women with hypertension and/or diabetes mellitus requiring an ACE inhibitor or angiotensin receptor blocker (ARB). Of these, 26 patients had a creatinine clearance >50 mL/min to <80 mL/min. Patients were given 1 mg estradiol (E2) and 3 mg drospirenone (DRSP) (n=112) or placebo (n=118) over 28 days. Non-diabetic patients also received ibuprofen 1200 mg/day for 5 days during the study. There was a single case of serum potassium >6.0 mEq/L and a single case of serum sodium <130 mEq/L on treatment, both occurring following five days of ibuprofen therapy in two women taking E2/DRSP. Serum potassium levels ≥5.5 mEq/L were observed in 8 (7.3%) E2/DRSP-treated subjects (3 diabetic and 5 non-diabetic) and in 3 (2.6%) placebo-treated subjects (2 diabetic and 1 non-diabetic). After 28 days of exposure, the mean change from baseline in serum potassium was 0.11 mEq/L for the E2/DRSP group and 0.08 mEq/L for the placebo group. None of the subjects with serum potassium levels ≥5.5 mEq/L had cardiovascular adverse events. A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium Cmax and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

Of note, occasional or chronic use of NSAID medication was not restricted in any of the **ANGELIQ** clinical trials.

Clinical Studies

Support for the indications
Support for treatment of vasomotor symptoms and vaginal and vulvar atrophy was shown through bioequivalence of the E2 component of the combination product with a currently marketed E2 product (Estrace®). The multiple-dose bioequivalence study evaluated the bioequivalence of E2 from a tablet containing DRSP (2 mg) and E2 (1 mg) relative to Estrace (1 mg) tablet. DRSP/E2 tablets met the criteria for bioequivalence to Estrace.

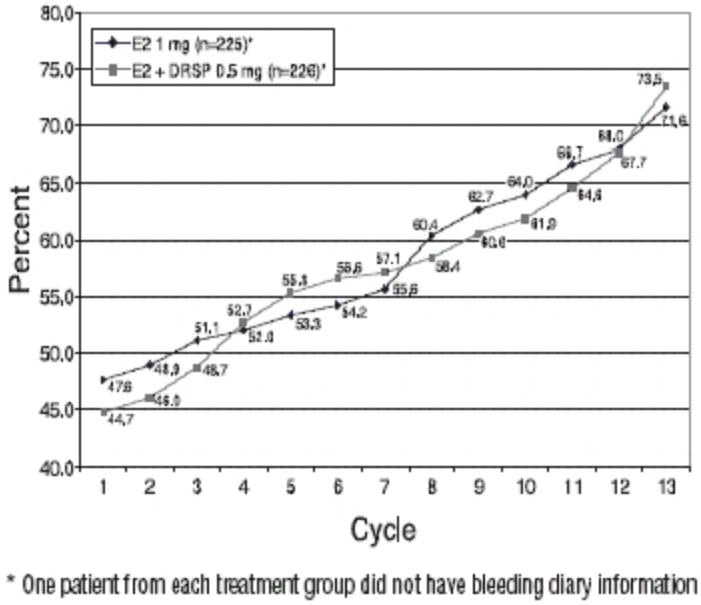
Effects on Endometrium
In a one year clinical trial of 1,142 postmenopausal subjects treated with E2 alone or E2 + 0.5, 1, 2, or 3 mg DRSP, endometrial biopsies were performed on 966 (84.6%) subjects during the treatment period. Eight subjects in the E2 monotherapy group developed endometrial hyperplasia (4 simple hyperplasia with no cytological atypia, 3 complex hyperplasia with no cytological atypia, and 1 complex hyperplasia with cytological atypia), and one subject in the 1 mg E2 + 2 mg DRSP group developed simple hyperplasia with no cytological atypia. Table 2 shows that there were no diagnoses of endometrial hyperplasia in the **ANGELIQ** group.

Table 2: Incidence of Endometrial Hyperplasia after up to 12 Months of Treatment

	E2 1 mg	**ANGELIQ**
Total No. Subjects	226	227

Total No. of On-Treatment Biopsies	197 (87.2%)	191 (84.1%)
Hyperplasia	8 (4.0%)	0 (0%)

Effects on Uterine Bleeding or Spotting
In a cumulative analysis performed over 12 months in a double blind trial, the proportions of women with amenorrhea increased and at one year, 73.5% of subjects on **ANGELIQ** had amenorrhea. Results are shown in Figure 2.



* One patient from each treatment group did not have bleeding diary information

Figure 2: Cumulative proportion of subjects with amenorrhea at a given cycle through cycle 13, LOCF

Women's Health Initiative Studies
The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of 0.625 mg conjugated equine estrogens (CE) per day alone or the use of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA sub-study was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the CE/MPA sub-study, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 3 below:

Table 3: Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI*

Event[c]	Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI†)	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02–1.63)	30	37

Non-fatal MI	1.32 (1.02–1.72)	23	30
CHD death	1.18 (0.70–1.97)	6	7
Invasive breast cancer ‡	1.26 (1.00–1.59)	30	38
Stroke	1.41 (1.07–1.85)	21	29
Pulmonary embolism	2.13 (1.39–3.25)	8	16
Colorectal cancer	0.63 (0.43–0.92)	16	10
Endometrial cancer	0.83 (0.47–1.47)	6	5
Hip fracture	0.66 (0.45–0.98)	15	10
Death due to causes other than the events above	0.92 (0.74–1.14)	40	37
Global Index §	1.15 (1.03–1.28)	151	170
Deep vein thrombosis ¶	2.07 (1.49–2.87)	13	26
Vertebral fractures ¶	0.66 (0.44–0.98)	15	9
Other osteoporotic fractures ¶	0.77 (0.69–0.86)	170	131

*****adapted from JAMA, 2002; 288:321–333
†nominal confidence intervals unadjusted for multiple looks and multiple comparisons
‡includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
§a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
¶not included in Global Index

For those outcomes included in the "global index," absolute excess risks per 10,000 person-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

The absolute excess risk of events included in the "global index" was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality. (See Boxed Warnings , Warnings, and Precautions.)

Women's Health Initiative Memory Study
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See Boxed Warnings and Warnings, 3. Dementia.)

INDICATIONS AND USAGE
ANGELIQ is indicated in women who have a uterus for the:
1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

CONTRAINDICATIONS
Progestogens/estrogens should not be used in individuals with any of the following conditions:
1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Renal insufficiency.
7. Liver dysfunction or disease.
8. Adrenal insufficiency.
9. **ANGELIQ** should not be used in patients with known hypersensitivity to its ingredients.
10. Known or suspected pregnancy. There is no indication for **ANGELIQ** in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See Precautions).

WARNINGS

ANGELIQ contains 0.5 mg of the progestin drospirenone that has antialdosterone activity, including the potential for hyperkalemia in high-risk patients.

ANGELIQ should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction, and adrenal insufficiency).

Use caution when prescribing ANGELIQ to women who regularly take other medications that can increase potassium, such as NSAIDs, potassium-sparing diuretics, potassium supplements, ACE inhibitors, angiotensin-II receptor antagonists, and heparin. Consider checking serum potassium levels during the first treatment cycle in high-risk patients.

See Boxed Warnings .

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately

a. Coronary heart disease and stroke

In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving oral CE compared to placebo. (See Clinical Pharmacology, Clinical Studies sections.)

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA-0.625mg/2.5mg per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years.

Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. (See Clinical Pharmacology and Clinical Studies sections.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in

the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Endometrial cancer
The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer
The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see Clinical Pharmacology,Clinical Studies). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01–1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, and risk factors, and prior mammogram results.

3. Dementia
In the estrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, 2,947 hysterectomized women aged 65 to 79 years were randomized to CE or placebo.
In the estrogen plus progestin WHIMS substudy, 4,532 postmenopausal women aged 65 to 79 years were randomized to CE/MPA or placebo. In the estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83–2.66). The absolute risk of probable dementia for estrogen alone versus placebo was 37 versus 25 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See Clinical Pharmacology, Clinical Studies and Precautions, I. GERIATRIC USE .)
After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence

interval 1.21–3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of proba
ble dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See Clinical Pharmacology, Clinical Studies and Precautions, I. GERIATRIC USE .)

4. Gallbladder disease
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual abnormalities
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. GENERAL

1. Addition of a progestin when a woman has not had a hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. Elevated blood pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia
In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

The clearance of drospirenone was decreased in patients with moderate hepatic impairment.

5. Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention
Because estrogen and estrogen/progestin therapy may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia
Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Hyponatremia
As an aldosterone antagonist, drospirenone may increase the possibility of hyponatremia in high-risk patients.

9. Ovarian cancer
The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77–3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

10. Exacerbation of endometriosis
Endometriosis may be exacerbated with administration of estrogens.

11. Exacerbation of other conditions
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas, and should be used with caution in women with these conditions.

B. PATIENT INFORMATION
Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe **ANGELIQ**.

C. LABORATORY TESTS
Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

D. DRUG/LABORATORY TEST INTERACTIONS
1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII–X complex, II–VII–X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG)) leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See Boxed Warnings , Warnings and Precautions.)
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See Boxed Warnings , Contraindications, and Warnings sections.)
In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.24 to 10.3 times the exposure (AUC of drospirenone) of women taking a 1 mg dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 2.3 to 51.2 times the exposure of women taking a 1 mg dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. (See Warnings section.)

F. PREGNANCY
ANGELIQ should not be used during pregnancy. (See Contraindications.)

G. NURSING MOTHERS
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when **ANGELIQ** is administered to a nursing woman.
After administration of an oral contraceptive containing drospirenone about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

H. PEDIATRIC USE
ANGELIQ is not indicated in children.

I. GERIATRIC USE
There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing **ANGELIQ** to determine whether those over 65 years of age differ from younger subjects in their response to **ANGELIQ**.
In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women who were older than 70. (See Warnings, 3. Dementia.)

ADVERSE REACTIONS
See Boxed Warnings , Warnings, AND Precautions.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.
The following are adverse events reported with **ANGELIQ** occurring in >5% of subjects:
Table 4: Adverse Events Regardless of Drug Relationship Reported at a Frequency of >5% in a 1-year Double-blind Clinical Trial

ADVERSE EVENT	**E2 1 MG (N=226) n (%)**	**ANGELIQ (N=227) n (%)**
BODY AS A WHOLE		
Abdominal pain	29 (12.8)	25 (11)
Pain in extremity	15 (6.6)	19 (8.4)
Back pain	11 (4.9)	16 (7)
Flu syndrome	15 (6.6)	16 (7)
Accidental injury	15 (6.6)	13 (5.7)
Abdomen enlarged	17 (7.5)	16 (7)
Surgery	6 (2.7)	12 (5.3)
METABOLIC & NUTRITIONAL DISORDERS		
Peripheral edema	12 (5.3)	4 (1.8)
NERVOUS SYSTEM		
Headache	26 (11.5)	22 (9.7)
RESPIRATORY SYSTEM		
Upper respiratory infection	40 (17.7)	43 (18.9)
Sinusitis	8 (3.5)	12(5.3)
SKIN AND APPENDAGES		
Breast pain	34 (15.0)	43 (18.9)

UROGENITAL		
Vaginal hemorrhage	43 (19.0)	21 (9.3)
Endometrial disorder	22 (9.7)	4 (1.8)
Leukorrhea	14 (6.2)	3 (1.3)

The following additional adverse reactions have been reported with estrogen and or estrogen/progestin therapy:

1. Genitourinary system
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting, dysmenorrhea, increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

2. Breasts
Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

3. Cardiovascular
Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

4. Gastrointestinal
Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, increased incidence of gall bladder disease, pancreatitis, enlargement of hepatic hemangiomas.

5. Skin
Chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.

6. Eyes
Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system
Headache, migraine, dizziness, mental depression, chorea, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia.

8. Miscellaneous
Increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, anaphylactoid/anaphylactic reactions including urticaria and angioedema, hypocalcemia, exacerbation of asthma, increased triglycerides.

OVERDOSAGE

In cases of **ANGELIQ** overdose, monitor serum concentrations of potassium and sodium since drospirenone has antimineralocorticoid properties.
Serious ill effects have not been reported following acute ingestion of large doses of progestin/estrogen-containing oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

The dosage of **ANGELIQ** is one tablet daily. Women who are already using a product containing estrogen should stop taking that product before starting **ANGELIQ**.
Use of estrogen, alone or in combination with a progestin, should be limited to the lowest effective dose available and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see Boxed Warnings and Warnings sections). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.
The lowest effective dose of **ANGELIQ** has not been determined.

HOW SUPPLIED

ANGELIQ TABLETS (drospirenone and estradiol) 0.5 mg/1 mg are available as round, biconvex pink film-coated tablets embossed with "CK" inside a hexagon, and supplied in the following packaging:

3 blisters of 28 tablets NDC 50419-483-03

Storage Conditions

Store at 25° C (77° F); excursions permitted to 15–30° C (59–86° F) [See USP Controlled Room Temperature].

REFERENCES FURNISHED UPON REQUEST

PATIENT INFORMATION

September 2005

ANGELIQ® TABLETS

(drospirenone and estradiol)

(an"ju–le–k')

Read this **PATIENT INFORMATION** before you start taking **ANGELIQ** and read what you get each time you refill **ANGELIQ**. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ANGELIQ (a combination of estrogen and a progestin)?

Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens with or without progestins may increase your chances of getting heart attack, strokes, breast cancer, and blood clots. Using estrogens with or without progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with ANGELIQ.

What is ANGELIQ?

ANGELIQ is a medicine that contains two kinds of hormones, estrogen and progestin.

What is ANGELIQ used for?

ANGELIQ is used after menopause to:

•**reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your health care provider should talk regularly about whether you still need treatment with **ANGELIQ**.

•**treat moderate to severe dryness, itching, and burning in or around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with **ANGELIQ** to control these problems. If you use **ANGELIQ** only to treat dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who should not use ANGELIQ?

Do not use **ANGELIQ** if you have had your uterus removed (hysterectomy).

ANGELIQ contains a progestin to decrease the chances of getting cancer of the uterus. If you do not have a uterus, you do not need a progestin and you should not use **ANGELIQ**.

Do not start taking ANGELIQ if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your health care provider about whether you should take **ANGELIQ**.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **have kidney disease, liver disease, or disease of your adrenal glands.**
- **are allergic to ANGELIQ or any of its ingredients**. See the end of this leaflet for a list of ingredients in **ANGELIQ**.
- **think you may be pregnant**.

Tell your health care provider:

- **if you are breastfeeding.** The hormone in **ANGELIQ** can pass into your milk.

- **about all of your medical problems.** Your health care provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, hypertension (high blood pressure) or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take**, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how **ANGELIQ** works. **ANGELIQ** may also affect how your other medicines work.

- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How should I take ANGELIQ?

1. Take one tablet every day.

2. Estrogens should be used only as long as needed. The lowest effective dose of **ANGELIQ** has not been determined. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with **ANGELIQ**.

What are the possible side effects of ANGELIQ?

ANGELIQ is different from other hormonal medicines for menopausal symptoms because it contains drospirenone, and drospirenone may increase the potassium or lower the sodium in your blood.

You should not take **ANGELIQ** if you have kidney, liver or adrenal disease because these conditions may also increase the potassium in your blood. Some other medicines also increase potassium. If you regularly take another medicine that increases potassium levels, talk with your healthcare provider about whether **ANGELIQ** is right for you. In some situations, your healthcare provider may recommend testing your blood for potassium.

Less common but serious side effects include the following and should be discussed with your healthcare provider to assess your personal risks:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision

• Vomiting

Call your health care provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

• Headache

• Breast pain

• Irregular vaginal bleeding or spotting

• Stomach/abdominal cramps, bloating

• Nausea and vomiting

• Hair loss

Other side effects include:

• High blood pressure

• Liver problems

• High blood sugar

• Fluid retention

• Enlargement of benign tumors of the uterus ("fibroids")

• Vaginal yeast infection

These are not all the possible side effects of **ANGELIQ**. For more information, ask your health care provider or pharmacist.

What can I do to lower my chances of a serious side effect with ANGELIQ?

Talk with your health care provider regularly about whether you should continue taking **ANGELIQ**.

See your health care provider right away if you get vaginal bleeding while taking **ANGELIQ**.

Have a breast exam and mammogram (breast X-ray) every year unless your health care provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your health care provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of ANGELIQ.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use **ANGELIQ** for conditions for which it was not prescribed. Do not give **ANGELIQ** to other people, even if they have the same symptoms you have. It may harm them.

Keep ANGELIQ out of the reach of children

This leaflet summarizes the most important information about **ANGELIQ**. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about **ANGELIQ** that is written for health professionals. You can get more information by calling our toll free number (1-888-237-5394) or visit www.angeliq-us.com

What are the ingredients in ANGELIQ?

The active ingredients in **ANGELIQ** are drospirenone (a progestin) and estradiol. **ANGELIQ** also contains lactose monohydrate NF, corn starch NF, modified starch NF, povidone USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol NF, talc USP, titanium dioxide USP, and ferric oxide pigment NF.

Do not store above 86°F (30°C).

Manufactured for:
Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

6702400 US 80621990
March 2008

Angeliq 1's Trade Carton

NDC 50419-483-01
1 Unit
Rx Only

Angeliq® Tablets
(Drospirenone and Estradiol)
0.5 mg/1 mg
— 0.5 mg/1 mg
— 28 tablets
— oral